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(54) **Amine derivatives of anthracycline antibiotics and antibody conjugates thereof.**

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(57) Novel antineoplastic amine-containing derivatives and methods for synthesizing such derivatives of anthracycline antibiotics are disclosed. The derivatives are useful to prepare site-selectively attached therapeutic antibody-anthracycline antibiotic conjugates which retain substantial immunospecificity of the unconjugated antibody molecule. Using the conjugates, targeted delivery of the attached antineoplastic amine derivatives of anthracycline antibiotics is achieved in vivo. Such conjugates are thus therapeutically effective against a variety of neoplastic cellular disorders when administered in vivo. Methods for preparing the antibody conjugates and for use of the conjugates in vivo are also disclosed.



PARTIAL EUROPEAN SEARCH REPORT

Which under Rule 45 of the European Patent Convention
shall be considered, for the purposes of subsequent
proceedings, as the European search report

Application number

EP 88 40 1353

DOCUMENTS CONSIDERED TO BE RELEVANT																											
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)																								
X	<p>JOURNAL OF CHROMATOGRAPHY, vol. 288, 1984, pages 127-136, Elsevier Science Publishers B.V., Amsterdam, NL;</p> <p>P.A. SCOURIDES et al.: "Application of analytical and semi-preparative high-performance liquid chromatography to anthracyclines and bis-anthracycline derivatives"</p> <p>* Page 127, summary; page 129, figure 2; page 135, lines 1-24 *</p> <p>--</p>		C 07 H 15/252 A 61 K 31/70 C 07 K 15/00 A 61 K 39/395 A 61 K 47/00																								
X,D	<p>J. CHEM. SOC., CHEM. COMMUN., 1986, pages 659-661;</p> <p>R.T.C. BROWNLEE et al.: "The synthesis and characterization of a series of bis-intercalating bis-anthracyclines"</p> <p>* Page 660, column 1, compound (6); column 2, lines 1-4 *</p> <p>--</p>	1,2																									
INCOMPLETE SEARCH																											
<p>The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims.</p> <p>Claims searched completely: 1-28</p> <p>Claims searched incompletely:</p> <p>Claims not searched: 29-31</p> <p>Reason for the limitation of the search:</p> <p>Method for treatment of human or animal body by surgery or therapy (see Art. 52(4) of the European Patent Convention).</p>																											
<table border="1"> <tr> <td>Place of search</td> <td>Date of completion of the search</td> <td>Examiner</td> </tr> <tr> <td>THE HAGUE</td> <td>01-03-1990</td> <td>BRENNAN</td> </tr> <tr> <td colspan="2">CATEGORY OF CITED DOCUMENTS</td><td>T : theory or principle underlying the invention</td></tr> <tr> <td colspan="2">X : particularly relevant if taken alone</td><td>E : earlier patent document, but published on, or after the filing date</td></tr> <tr> <td colspan="2">Y : particularly relevant if combined with another document of the same category</td><td>D : document cited in the application</td></tr> <tr> <td colspan="2">A : technological background</td><td>L : document cited for other reasons</td></tr> <tr> <td colspan="2">O : non-written disclosure</td><td>& : member of the same patent family, corresponding document</td></tr> <tr> <td colspan="2">P : intermediate document</td><td></td></tr> </table>				Place of search	Date of completion of the search	Examiner	THE HAGUE	01-03-1990	BRENNAN	CATEGORY OF CITED DOCUMENTS		T : theory or principle underlying the invention	X : particularly relevant if taken alone		E : earlier patent document, but published on, or after the filing date	Y : particularly relevant if combined with another document of the same category		D : document cited in the application	A : technological background		L : document cited for other reasons	O : non-written disclosure		& : member of the same patent family, corresponding document	P : intermediate document		
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			TECHNICAL FIELDS SEARCHED (Int. Cl.4)
X	<p>CHEMICAL ABSTRACTS, vol. 87, no. 11, September 12, 1977, page 32-33, abstract no. 78376t, Columbus, Ohio, US;</p> <p>A. GOLDIN et al.: "Antitumor effect of adriamycin in comparison with related drugs, and in combination chemotherapy"</p> <p>& ADRIAMYCIN REV., EORTC INT. SYMP., 2nd 1974 (Pub. 1975), 37-54</p> <p>* ABSTRACT & FORMULA INDEX 1977-1981, vol. 86-95, pages 16374-16375, C₂₈H₃₃N₅O₁₀, Carbonic dihydrazide *</p> <p>--</p>	1,2	
X	<p>US-A-3 957 755 (G. JOLLES)</p> <p>* Column 1, line 6 - column 2, line 56 *</p> <p>--</p>	1,2	
X	<p>BE-A- 869 485 (INSTITUT INTERNATIONAL DE PATHOLOGIE CELLULAIRE)</p> <p>* Claim 1 *</p> <p>--</p>	17	
X,Y	<p>EP-A-0 088 695 (CYTOGEN)</p> <p>* Page 18, table 1; page 19, line 18 - page 22, line 5; page 28, line 1 - page 49, line 20; claims 1-6,10-13,22-30,36-41,45-50,54 *</p> <p>--</p>	18-28	
Y	<p>CHEMICAL ABSTRACTS, vol. 106, no. 2, January 12, 1987, page 280, abstract no. 9420b, Columbus, Ohio, US;</p> <p>& JP-A-61 155 334 (TEIJIN LTD.) 15-07-1986</p> <p>* Abstract *</p> <p>--</p>	18-28	
Y	<p>CHEMICAL ABSTRACTS, vol. 106, no. 13, March 30, 1987, page 695, abstract no. 102645p, Columbus, Ohio, US;</p> <p>& JP-A-61 254 598 (GREEN CROSS CORP.) 12-11-1986</p> <p>* Abstract *</p> <p>--</p>	18-28	



DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
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Y	INT. J. CANCER, vol. 33, 1984, pages 737-744; J.GALLEGO et al.: "Preparation of four daunomycin-monoclonal antibody 791T/36 conjugates with anti-tumour activity" * The whole article * --	18-28	
A,D	CHEMICAL ABSTRACTS, vol. 93, no. 24, December 15, 1980, page 313, abstr. no. 225585q, Columbus, Ohio, US; E.HURWITZ et al.: "Soluble macro- molecules as carriers for dau- norubicin" & J. APPL. BIOCHEM. 1980, 2(1), 25-35 * Abstract * -----	18-28	TECHNICAL FIELDS SEARCHED (Int. Cl 4)